I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on August 30, 2010.

Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 AND UNDER 37 CFR 1.323
Docket No. SER.109

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Mara Rossi
Issued	:	July 13, 2010
Patent No.	:	7,754,860
Conf. No.	:	3915
For	:	Method for Purifying FSH

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE) AND
UNDER 37 CFR 1.323 (APPLICANT MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Reads:**
Column 3, line 40:	Page 4, line 25:
"HOP: host cell protein"	--HCP: host cell protein--

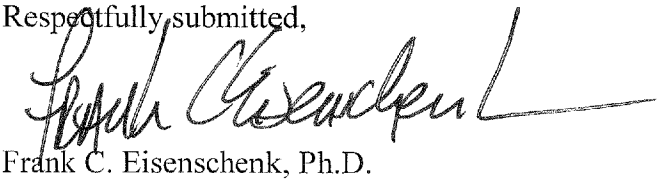
Column 3, line 42:	Page 4, line 26:
"IPO: In process controls"	--IPC: In process controls--
Patent Reads:	**Application Should Read:**
Column 8, line 20:	Page 12, line 2:
"50-56]."	--50-56.--
Column 15, line 53:	Page 24, line 31:
"than one days"	--than one day--
Column 16, line 63:	Page 26, line 34:
"than one days"	--than one day--
Column 18, line 35:	Page 29, last line in table:
"ultrafilterd"	--ultrafiltered--
Patent Reads:	**Application Reads:**
Column 24, line 4:	Amendment dated June 11, 2009 (original claim 22, renumbered as claim 20):
"about 013"	--about 0.13--.

A true and correct copy of page 4 of the specification and a copy of the Amendment Under 37 C.F.R. § 1.111 dated June 11, 2009 which support Applicant's assertion of the errors on the part of the Patent Office accompanies this Certificate of Correction.

The fee of $100.00 was paid at the time this Request was filed. The Commissioner is also authorized to charge any additional fees as required under 37 CFR 1.20(a) to Deposit Account No. 19-0065.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,



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Attachments: Copy of page 4 of the specification
Copy of Amendment Under 37 C.F.R. § 1.111
Certificate of Correction

Figure 2 shows the elution profile for chromatography of crude rhFSH on Q Sepharose FF as detected by OD at 280 nm

Figure 3 shows the elution profile for IMAC chromatography of partially purified rhFSH as detected by OD at 280 nm.

Figure 4 shows the elution profile for DEAE Sepharose chromatography of partially purified rhFSH as detected by OD at 280 nm.

Figure 5 shows the elution profile for Phenyl Sepharose chromatography of partially purified rhFSH as detected by OD at 280 nm.

Figure 6 shows the elution profile for the RPC step using a Source 30 RPC column.

Abbreviations

The following abbreviations are used in the description of the invention:

FSH: follicle stimulating hormone;

rFSH: recombinant FSH;

hFSH: human FSH;

rhFSH: recombinant human FSH

BV: Bed volume

DEAE: diethylaminoethyl

IMAC: immobilised metal ion affinity chromatography

OD: optical density

HIC: Hydrophobic interaction chromatography

HPLC : high performance liquid chromatography

IRMA: immunoradiometric assay

KD or kD: kiloDalton

HCP: host cell protein, proteins arising from the host cell used for expression of FSH

IPC: In process controls

RP-HPLC: reverse phase high performance liquid chromatography

Q FF: anion exchange on Q sepharose FF

Detailed description of the invention

The invention provides a method for purifying recombinant human FSH or an FSH variant, comprising the steps:

(1) ion exchange chromatography;

(2) immobilised metal ion chromatography;

(3) hydrophobic interaction chromatography (HIC).

which may be carried out in any order.

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on June 11, 2009.

Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

AMENDMENT UNDER 37 C.F.R. § 1.111
Patent Application
Docket No. SER.109

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Christina M. Borgeest, Ph.D.
Art Unit	:	1649
Applicant	:	Mara Rossi
Serial No.	:	10/581,172
Filed	:	February 6, 2007
Conf. No.	:	3915
For	:	Method for Purifying FSH

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

In response to the Office Action dated March 18, 2009, please amend the above-identified patent application as follows:

In the Claims

1 (currently amended). A method for purifying recombinant human follicle stimulating hormone (FSH) or an FSH variant comprising the steps of subjecting FSH to:

(1) ion exchange chromatography at a pH of about 8.5;

(2) immobilised metal ion chromatography at a pH of about 9 ; and

(3) hydrophobic interaction chromatography (HIC) at a pH of about 8.25.

2 (original). The method of claim 1, wherein the ion exchange chromatography is carried out with a strong anion exchange resin.

3 (currently amended). The method of claim 2, wherein the anion exchange resin is a quaternary ammonium chromatography resin~~Q Sepharose FF, or a resin having similar properties~~.

4 (previously presented). The method of claim 1, wherein the ion exchange chromatography is carried out using borate buffer as eluent.

5 (original). The method of claim 4, wherein the borate buffer is at a pH of at or about 8.5.

6 (previously presented). The method of claim 1, wherein the immobilised metal ion chromatography is carried out with a resin having tridentate chelating groups.

7 (original). The method of claim 6, wherein the chelating groups are iminodiacetic acid.

8 (canceled).

9 (previously presented). The method of claim 1, wherein the immobilised metal ion chromatography is carried out with a metal ion selected from Cu^{2+}, Zn^{2+}, Ni^{2+}, Ca^{2+}, Mg^{2+} and Co^{2+}.

10 (previously presented). The method of claim 1, wherein the immobilised metal ion chromatography is carried out with Cu^{2+}.

11 (previously presented). The method of claim 1, wherein the immobilised metal ion chromatography is carried out using ammonium acetate as eluent.

12 (original). The method of claim 11, wherein the ammonium acetate buffer has a pH ~~of~~ at or about 9.

13 (currently amended). The method of claim 1, wherein the hydrophobic interaction chromatography (HIC) is carried out using chromatography resin comprising phenyl groups~~Phenyl Sepharose FF HS, or a resin having similar characteristics~~.

14 (previously presented). The method of claim 1, wherein the hydrophobic interaction chromatography is carried out using ammonium acetate (50 mM) /ammonium sulphate (0.25 M) as eluent.

15 (currently amended). A method for purifying recombinant human follicle stimulating hormone (FSH) or an FSH variant comprising the steps of subjecting FSH to:

(1) ion exchange chromatography;

(2) immobilised metal ion chromatography;

(2a) ion exchange chromatography; and

(3) hydrophobic interaction chromatography (HIC)~~The method of claim 1, comprising a second step of ion exchange chromatography (2a)~~, wherein a second step of ion exchange

chromatography (2a) is carried out after the step of immobilised metal ion chromatography, and before the step of hydrophobic interaction chromatography (HIC).

16 (original). The method of claim 15, wherein the second step of ion exchange chromatography is carried out using a weak anion exchange resin.

17 (currently amended). The method of claim 16, wherein the weak anion exchange resin comprises diethylaminoethyl groups~~is DEAE Sepharose FF resin, or a resin having similar properties~~.

18 (previously presented). The method of claim 1, further comprising a step of reverse phase chromatography (4), carried out after the step of hydrophobic interaction chromatography (HIC).

19 (canceled).

20 (currently amended). The method of~~claim 19~~ claim 18, wherein the reverse phase chromatography is carried out using a solution comprising ammonium acetate (50 mM, pH at or about 7.6) with 20% (v/v) 2-propanol.

21 (previously presented). The method of claim 18, comprising a step of ultrafiltration (5), carried out after the step of reverse phase chromatography.

22 (currently amended). A method for purifying human recombinant ~~FSH~~ follicle stimulating hormone (FSH) comprising the steps of subjecting FSH to:

(i) ultrafiltration;

(ii) anion exchange chromatography on ~~Q Sepharose FF~~a resin comprising quaternary ammonium groups with a solution comprising ~~at or~~ about 50 mM borate, ~~at or~~ about 0.13 M NaCl, ~~pH at or~~ at a pH of about 8.5 as eluent;

(iii) subjecting the eluate of step (ii) to a step of immobilised metal ion affinity chromatography on ~~chelating Sepharose ffFF~~a resin comprising tridentate chelate groups, with Cu^{++} as metal ion, ~~and at or~~ with an solution of about 0.75 M ammonium acetate ~~pH at or about 9~~ at a pH of about 9 as eluent;

(iv) subjecting the eluate of step (iii) to a step of anion exchange chromatography on a resin comprising diethyldiaminoethyl groups~~DEAE Sepharose FF~~, with a solution comprising ~~at or~~ about 0.11 M Ammonium acetate, ~~pH at or~~ pH of about 8.5 as eluent;

(v) subjecting the eluate of step (iv) to a step of hydrophobic interaction chromatography on a chromatography resin comprising phenyl groups~~Phenyl Sepharose FF HS~~ with ~~at or~~ a solution comprising about 50 mM ammonium acetate, ~~at or~~ about 0.25 M ammonium sulphate, at a pH of ~~pH at or~~ about 8.25 as eluent;

(vi) subjecting the eluate of step (v) to a step of reverse phase chromatography on a reverse phase chromatography resin~~Source 30 RPC~~, with ~~at or~~ a solution comprising about 50 mM ammonium acetate, pH of about~~at or about~~ 7.6, and ~~with at or~~ about 20% of 2-propanol (v/v);

(vii) subjecting the eluate of step (vi) to a step of ultrafiltration; and

(viii) subjecting the retentate of step (vii) to a step of nanofiltration.

23-24 (canceled).

25 (withdrawn-currently amended). A composition of matter comprising:

(a) a purified recombinant human ~~FSH~~ follicle stimulating hormone (FSH) or FSH variant produced by the process of claim 1; or

(b) a composition comprising a purified recombinant human FSH or FSH variant produced by the process of claim 1 and a liquid.

26 (withdrawn-previously presented). The composition of matter of claim 25, wherein said liquid is a buffer, stabilizer or an excipient.

27 (new). The method of claim 1, comprising a second step of ion exchange chromatography (2a), carried out after the step of immobilised metal ion chromatography, and before the step of hydrophobic interaction chromatography (HIC).

28 (new). The method of claim 27, wherein the second step of ion exchange chromatography is carried out using a weak anion exchange resin.

29 (new). The method of claim 28, wherein the weak anion exchange resin comprises diethylaminoethyl groups.

Remarks

Claims 1-22, 25 and 26 are pending in the subject application. Applicants acknowledge that claims 25-26 have been withdrawn from further consideration as being drawn to a non-elected invention. Applicants gratefully acknowledge the Examiner's indication that claims 15-22 are free of the prior art. By this Amendment, Applicants have canceled claims 8 and 19, amended claims 1, 3, 13, 15, 17, 20, 22 and 25 and added new claims 27-29. Support for the amendments can be found throughout the subject specification and in the claims as originally filed (see, for example, pages 4-7 of the as-filed description and previously pending claims 15-17). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-7, 9-18, 20-22, and 25-29 are currently before the Examiner with claims 25 and 26 standing withdrawn from consideration. Favorable consideration of the pending claims is respectfully requested.

At the outset, Applicants respectfully submit that claim 15, reformulated as an independent claim in this response, reads on the particular order of steps as recited in previously pending claim 15. This claim has been acknowledged to be neither disclosed nor suggested in the cited prior art (see page 11 of the Office Action dated March 18, 2009).

Claims 1, 6, 8-11, 13-15, 21 and 22 are objected to because of informalities. Specifically, claims 1 and 22 are objected to because the term "FSH" should be spelled out for the first instance of use and claim 22 is objected to because the term "ff" should be capitalized. Applicants gratefully acknowledge the Examiner's careful review of the claims. However, Applicants note that the acronym "FSH" is spelled out before its initial use in claim 1. In accordance with the Examiner's suggestion, claim 22 has been amended to recite "follicle stimulating hormone" with the acronym "FSH" in parentheses and the word "ff" has been replaced in claim 22 with generic terminology for the chromatography media originally recited in the claim. In addition, withdrawn claim 25 has been amended. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 6, 8-11, 13-15, 18 and 21 are objected to under 37 CFR §1.75(c) as being of improper dependent form because a multiple dependent claim cannot depend from any other multiple dependent claim. Applicants respectfully assert that there are no multiple dependent claims in the presently pending claim set. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 3-22 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite because claims 3, 8, 13, 17, 19 and 22 contain the trademark/trade name Sepharose. Applicants respectfully assert that the claims as filed are definite; however, by way of this response, the claims have been canceled or amended to recite chromatography resins containing the functional groups associated with the resins recited in the original claims. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 1-3 and 6-14 are rejected under 35 U.S.C. § 103(a) as obvious over Wolfenson *et al.* (2000) in view of Chiba *et al.* (1997). The Office Action states that Wolfenson *et al.* teach purification of gonadotropins using a scheme outlined on the title page that comprises two ion exchange chromatography steps followed by two hydrophobic interaction chromatography (HIC) steps. The Office Action also states that Wolfenson *et al.* describe that the ion exchange chromatography can be carried out with a strong anion exchange resin and suggest the use of the Q Sepharose and that the HIC can be carried out using the Phenyl-Sepharose resin. The Office Action indicates that Chiba *et al.* teach purification of FSH using affinity chromatography followed by immobilized metal ion affinity chromatography and HIC. The Office Action states that Chiba *et al.* further teach that the metal ion affinity chromatography is carried out with a resin having tridentate chelating groups that are iminodiacetic acid and Cu^{2+} and that the metal ion chromatography is carried out with a resin having similar properties to chelating Sepharose FF, which outline conditions similar to those described at p. 207, left column, 1st paragraph (*e.g.*, tridentate chelate groups such as iminodiacetic acid and Cu^{2+}). The Office Action notes that Wolfenson *et al.* fail to teach a purification step comprising metal ion affinity chromatography and turns to Chiba *et al.* to remedy this defect in the teachings of Wolfenson *et al.* The Office Action also notes that claims 11 and 12 recite that the metal ion chromatography eluted with ammonium acetate at a pH of at or about 9 and claim 14 recites that the HIC is eluted with ammonium acetate (50 mM)/ammonium sulfate(0.25M). The Office Action argues that:

> [a]lthough neither of the references teach these precise conditions, they do teach these buffers as eluents. Wolfenson et al. teach about 50mM ammonium acetate (pH 7) as an eluent for ionic exchange chromatography. Wolfenson et al. teach 0.4 - 1.2 M ammonium sulfate as an eluant for HIC at p. 9, 1st paragraph. Chiba et al. teach also teach ammonium sulfate (1.7M) as an eluent for HIC at p. 207, left column last

paragraph through right column, 1st paragraph. Note also that claim 12 recites "at or about a pH of 9", therefore, a pH of 7 can reasonably be interpreted as "at or about." Given that the recited buffers are standard buffers used in chromatography and that choice of buffers can be optimized as part of routine experimentation (i.e., no undue burden is placed on one of ordinary skill in the art to optimize conditions), the differences in buffers and concentration recited in these claims are not enough to support patentability. See MPEP 2144.05:

> A. Optimization Within Prior Art Conditions or Through Routine Experimentation
>
> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70%> was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).
>
> It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Wolfenson et al. by adding a step using metal ion chromatography in the purification scheme, as taught in Chiba et al. because Chiba et al. identified a shortcoming of ion exchange chromatography that was recognized in the art at the time, namely, that it cannot achieve

> complete separation of gonadotropins because of charge heterogeneity (see p. 205, right column). Thus Chiba et al. proposed a purification scheme using affinity chromatography followed by metal ion affinity chromatography and HIC in order to remedy the problem. The person of ordinary skill in the art would have been motivated to combine the teachings for several reasons. First, Chiba et al. identified for the person of ordinary skill in the art the limitations of the well known method of ion exchange chromatography, thus the artisan had guidance as to the problem, as well as a possible solution. Second, one of ordinary skill in the art would have been motivated to combine purification schemes to prepare a purer FSH product. FSH is used in treatment of infertility, and there is strong motivation in the art to have pure product in treatment regimens, as outlined in the first 3 pages of Wolfenson et al. Third, in protein purification, there are a finite number of predictable methods in order to achieve a result, namely, ion exchange chromatography, HIC and affinity chromatography.

Applicants respectfully assert that the claimed invention is not obvious over the cited references and traverse the rejection of record.

It is fundamental patent law that an obviousness rejection fails if the prior art relied on does not disclose all of the limitations of the claimed invention. *See, e.g., In re Zurko*, 258 F.3d 1379, 1385-86 (Fed. Cir. 2001). Thus, obviousness requires a teaching or suggestion of all limitations in a claim. *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974)). Furthermore, as the Supreme Court stated, "*there must be some articulated reasoning* with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added)).

At the outset, Applicants respectfully submit that the Office Action fails to establish a *prima facie* case of obviousness for the claimed invention. Applicants further note that the Office Action cites to M.P.E.P §2144.05 for support for the proposition that "differences in buffers and concentrations recited in the claims are not enough to support patentability". Applicants also note that the Office Action does not reference M.P.E.P §2144.05(II)(B) where it is stated:

B. Only Result-Effective Variables Can Be Optimized

> A particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 U.S.P.Q. 6 (C.C.P.A. 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.).

In this case, the Office Action has failed to establish that the pH of the elution buffers were "recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation". Thus, it is respectfully submitted that a *prima facie* case of obviousness has not been established by the cited combination of references.

Even assuming that the Patent Office is able to establish that the pH of elution buffers is "recognized as a result-effective variable", the Board of Patent Appeals and the predecessor of the Court of Appeals for the Federal Circuit (the Court of Customs and Patent Appeals) have held that it would not have been obvious for one of ordinary skill in the art to find an optimum value that is far outside the range taught by the prior art. *See In re Sebek*, 465 F.2d 904, 907 (C.C.P.A. 1972). *See also, e.g.*, *Ex parte Atkinson*, Appeal 2007-3900 ("optimization of a known result-effective variable in a given range is generally obvious only when it is reasonably expected that an improvement will arise in that range") (reversing Examiner's optimization-based obviousness rejection; internal citation omitted). In this case, Applicants note that the pH of the buffers recited in the currently pending claims are far outside the concentrations taught or suggested by Wolfenson *et al.* and/or Chiba *et al.* and are basic buffers as compared to the acidic or neutral buffers taught within each of the cited references. The following table sets forth the pH values of the various buffers used for the purification of FSH within the cited references and as recited in the claims:

Step	Claims	Wolfenson	Chiba
Ion exchange chromatography	About 8.5	5.0 (see Example 1, pages 14-16)	Not taught or performed
Immobilized metal ion chromatography	About 9	Not taught or performed	4.2 (see Figure 3)

Hydrophobic interaction chromatography	About 8.25	5.0 (see Example 1, pages 14-16)	4.2 or 7.0 (see Figures 1 and 5)

Applicants note that Wolfenson *et al.* indicate that the elution buffers disclosed in the application can have a pH between 5.0 and 7.0; however, the Examples only provide evidence for eluting FSH with buffers having a pH around 5.0 to 5.1 (see pages 15-16). Applicants further note that Chiba *et al.* indicate that the use of acidic conditions for the purification of FSH via HIC results in the separation of FSH from contaminating proteins that co-elute with FSH at neutral pH (see page 216, column 2, lines 3-11). Thus, it is clear that the claimed pH ranges are far outside those taught within the references as resulting in the elution of FSH from the various chromatography resins recited within the claims and that one of ordinary skill in the art would not have had a reasonable expectation of success in purifying FSH from contaminating proteins via HIC when using buffers having a neutral pH.

Applicants further note the argument that the term "about" allows the Patent office to reasonably interpret a pH of 7 as a pH at or about 9 (Office Action at page 6). Applicants respectfully disagree. Terms such as "about" must be given reasonable scope and such terms must be viewed as they would be understood by persons experienced in the field of the invention and as it would be understood in the light of the technology embodied in the invention. *Modine Mfg. Co. v. United States International Trade Commission*, 75 F. 3d 1545, 1554, 37 USPQ2d 1609, 1615 (Fed. Cir. 1996) citing *Andrew Corp. v. Gabriel Electronics, Inc.*, 847 F.2d 819, 821-22, 6 USPQ2d 2010, 2013 (Fed. Cir.), cert. denied, 488 U.S. 927 (1988). In the present instance, the Examiner has provided no showing as to why one of ordinary skill would understand a pH of 7 (*i.e.*, a neutral pH) as approximately the same as a basic (alkali) pH of 9 and it is respectfully submitted that one skilled in the art would not understand a pH of about 9 to be the same as a pH of 7 in the field of column chromatography. "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); *see also KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127

S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). Accordingly, reconsideration and withdrawal of the rejection of record is respectfully requested.

Claims 4 and 5 are rejected under 35 U.S.C. § 103(a) as obvious over Wolfenson *et al.* (2000) in view of Chiba *et al.* (1997) and further in view of Tikhomirov *et al.* (1978). The Office Action argues that Tikhomirov *et al.* teach borate buffer as an eluent at a pH of about 8.5 in a procedure to separate and determine amino acids, amino sugars and neutral carbohydrates and that it would have been appropriate to modify the buffers of both Wolfenson *et al.* and Chiba *et al.* such that the pH of the buffers would have been about 8.5. The Office Action further argues that Tikhomirov *et al.* taught a chromatographic method that was optimized for glycoproteins (see page 10 of the Office Action) and that the person of skill in the art would have been motivated to substitute the buffers of Tikhomirov *et al.* for those of Wolfenson *et al.* and Chiba *et al.* Applicants respectfully submit that one skilled in the art would not have been motivated to substitute the buffers of Tikhomirov *et al.* for those of Wolfenson *et al.* and Chiba *et al.* and traverse the rejection of record.

At the outset, it is noted that Tikhomirov *et al.* do not teach "a chromatographic method that is optimized for glycoproteins". As correctly noted earlier in the Office Action (at page 9), the methods of Tikhomirov *et al.* relate to "a procedure to separate and determine amino acids, amino sugars and neutral carbohydrates (see abstract; p. 200, Table I). In the abstract they teach '[s]tepwise elution systems with sodium citrate and borate buffers have developed for the ion exchange liquid chromatographic separation of amino acids and sugars ... With the aid of this system, the direct quantitative comparison of sugars and amino acids by liquid chromatography becomes possible for the first time." The Office Action makes a conclusory argument, in the sentence bridging pages 9-10, that "[t]heir teachings illustrate the high level of skill in the art (i.e., the ability of the person of ordinary skill to optimize conditions) and that they developed a method that was ideal for glycoproteins, which contain sugars and amino acids". As noted above, rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

Applicants further submit that one skilled in the art would not have been motivated to utilize buffers taught in Tikhomirov *et al.* in view of the teachings of Wolfenson *et al.* and Chiba *et al.* As noted above, Wolfenson *et al.* and Chiba *et al.* both teach the use of acidic buffers for the purification of FSH from related proteins. Indeed, the examples of Wolfenson *et al.* do not teach the use of a buffer having a pH higher than about 5.1 and Chiba *et al.* indicate that attempts to purify FSH via HIC using neutral buffers results in a FSH preparation that is contaminated by co-eluting proteins (see page 216, column 2, lines 3-11). Chiba *et al.* further teach that FSH can be separated from the co-eluting protein contaminants via the use of acidic buffers (buffers having a pH of 4.2) and there is nothing in the cited combination of references that would have led one of ordinary skill in the art to modify the teachings of Chiba *et al.* and/or Wolfenson *et al.* such that non-acidic buffers (*i.e.*, neutral or basic (alkali) buffers) would have been used to purify FSH. As noted in the Office Action, Tikhomirov *et al.* was added to the combination of Wolfenson *et al.* and Chiba *et al.* in an effort to cure an acknowledged deficit in their combined teachings, namely the use of a borate buffer at a pH of about 8.5. As noted by the Supreme Court, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S.Ct at 1741. Accordingly, it is respectfully submitted that the cited combination of references does not render the claimed invention obvious and reconsideration and withdrawal of the rejection of record is respectfully requested.

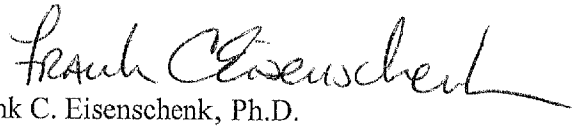
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,754,860

APPLICATION NO.: 10/581,172

DATED : July 13, 2010

INVENTOR : Mara Rossi

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 3,
Line 40, "HOP: host cell protein" should read --HCP: host cell protein--.
Line 42, "IPO: In process controls" should read --IPC: In process controls--.

Column 8,
Line 20, "50-56]." should read --50-56.--.

Column 15,
Line 53, "than one days" should read --than one day--.

Column 16,
Line 63, "than one days" should read --than one day--.

Column 18,
Line 35, "ultrafilterd" should read --ultrafiltered--.

Column 24,
Line 4, "about 013" should read --about 0.13--.

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